Improving glucocorticoid replacement profiles in adrenal insufficiency

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Improving glucocorticoid replacement profiles in adrenal insufficiency

Glucocorticoid replacement in AI

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Conflict of Interest:

None of the authors declare a conflict of interest.

Summary:

There is an increased mortality associated with adrenal insufficiency despite glucocorticoid replacement therapy with a standardised mortality ratio greater than two. The cause of the increased mortality is yet to be definitively elucidated, but may be due to excess steroid exposure, or replacement regimens that are uncoupled from the normal physiological cortisol profile. Cortisol secretion follows an ultradian pattern which is not possible to reproduce using oral replacement. With the advent of new pumps, it is now possible to mimic the pulsatility of the adrenal glands. Whilst the cognitive and emotional benefits of reproducing the ultradian rhythm is known, the presence of long-term benefits are not yet clear.

There is a dearth of evidence and high-quality studies to underline our current understanding of the pathophysiology of adrenal insufficiency and replacement therapy. There is a particular lack of research comparing objective outcomes between patients receiving hydrocortisone replacement (either standard therapy or new sustained release preparations), prednisolone replacement, and ultradian pumps. Direct comparative studies are now warranted to understand the optimal approach.

Keywords:

Adrenal insufficiency, hypocortisolism, glucocorticoids, cortisol, hydrocortisone, prednisolone.

Main Text:

There is no doubt that steroid replacement with glucocorticoids saves lives in patients with adrenal insufficiency, a condition with an associated mortality of 100% before the development of glucocorticoids[1]. Excess glucocorticoid exposure, as evidenced by patients with Cushing's syndrome, can also be fatal. Remarkably however, there is no agreement on how we can optimise replacement therapy for either primary or secondary adrenal insufficiency. Several options result in excess glucocorticoid exposure, which may reduce the risk of an Addisonian crisis, but only at the cost of a reduced natural killer cell function[2], an increased cardiovascular disease burden[3,4], and increased mortality[5]. Whether the increased mortality is the result of excessive exposure to glucocorticoid, or inappropriate timing and rhythm of replacement remains unclear.

The importance of circadian rhythmicity has been clear for a long time and life forms from primitive cyanobacteria, through all phyla to man, have adapted to this with mechanisms to predict the changing environments of the 24-hour day. Uncoupling glucocorticoid dose timing from the normal circadian cortisol rhythm is harmful[6,7] and human cells have developed circadian clocks that are, to varying extents, kept in synchrony by the HPA axis [8]. Cortisol levels rise at around 4am, under the influence of the central circadian pacemaker in the hypothalamic suprachiasmatic nucleus. This activates or inhibits a massive variety of genes in all tissues of the body, in anticipation of the body's needs at awakening and can also alter the endogenous clock gene "setting" of cells [9]. Misalignment between cortisol levels and clock time is one of the factors contributing to the adverse health outcomes seen in shift workers and problems associated with jet lag [10].

Oral preparations of glucocorticoids

The excess replacement that frequently occurs with twice or thrice daily hydrocortisone is associated with an increase in cardiovascular deaths in these patients, especially with escalating doses [4] and the late peaks in cortisol might be harmful [11]. A delayed release preparation (Chronocort) taken last thing at night [12] has the theoretical advantage of mimicking the early morning 4am rise in cortisol, which cannot be achieved with other preparations. Chronocort has already shown potential to suppress morning and 24-hour androsteinedione levels in patients with congenital adrenal hyperplasia during phase II trials[13], but more studies are needed to determine the clinical importance of this anticipatory rise in cortisol.

Another strategy available in some countries is the use of dual release hydrocortisone (Plenadren) once daily first thing in the morning. This sustained release preparation fails to replicate the pre-awakening rise in cortisol and we know very little about what happens to blood or tissue levels of cortisol overnight. It relies on continuous absorption of hydrocortisone from the gut which can be variable, a problem that must be guarded against in patients with infectious diarrhoea, when glucocorticoids are crucial [14]. The manufacturers state that Plenadren is commonly associated (> 1 in 10 cases) with gastrointestinal side effects [15].

Building on the early comparative findings that Plenadren may lower blood pressure, weight and improve HbA1c compared to multiple daily cortisone acetate or hydrocortisone[16], the DREAM study undertook a similar comparison[17]. Although the primary outcome focussed on weight change, the DREAM study also looked at the effect of Plenadren on immune profiles. Recruiting 89 patients on multiple daily cortisone acetate or hydrocortisone, the investigators switched 46 patients to

Plenadren and asked 43 to continue on the thrice daily immediate release preparations. A third group of 25 healthy volunteers were also recruited and data collected over a 24-week follow up period. In addition to a significant corrected weight loss of 4Kg in the switch group, the investigators reported significantly higher classical (CD14+CD16-) monocytes, with lower non-classical (CD14-CD16+) monocytes and CD16+ mature natural killer cells in patients taking thrice-daily hydrocortisone at baseline versus the healthy volunteers. Converting patients to once daily Plenadren was associated with improved numbers of the classical and non-classical monocytes and the mature natural killer cells, with concordant decreases in the soluble CD16 immune marker (an indicator of natural killer cell immaturity) and reported rates of infection as measured by a questionnaire[17]. These finding suggest that Plenadren may be less immunosuppressive than multiple daily dosing of glucocorticoids and that leucocytes may hold the key to assessing the adequacy of an individual's glucocorticoid replacement therapy. Because a majority of the patients were on cortisone acetate, it is not clear whether the variable metabolism of cortisone to cortisol might be a factor.

A DREAM ancillary study also investigated the effect of the switch to Plenadren on the RNA expression of clock genes. The analysis found that 19 of 68 different clock genes were differently expressed at baseline in all patients taking thrice daily hydrocortisone compared to the healthy volunteer control group[18]. In the switch group, the expression of 18 of the 19 affected genes were found to normalised to the levels seen within the healthy volunteers over 12 weeks. Clock genes are involved in auto-regulated feedback cycles thought to be responsible for conveying clock time to individual tissues and cells. The oscillations of clock genes regulate and control the transcription of proteins and can inform tissue sensitivity to glucocorticoids depending on the time of day, through acetylation of lysine residues on the glucocorticoid receptor[6,19]. Although dissociation of peripheral clock genes and the central suprachiasmatic clock is associated with disease states, the functional significance is not understood[19]. The physiological improvements demonstrated by Plenadren have been attributed to its ability to better mirror the natural circadian cortisol profile, compared to multiple daily hydrocortisone or cortisone acetate although this association might simply be due to the lower steroid exposure seen with Plenadren, with data indicating a reduction of approximately 20% in area-under-the curve exposure[16].A majority of the patients were on cortisone acetate, which depends on hepatic activation by 11β hydroxysteroid dehydrogenase (11βHSD1) to cortisol[20]. It was assumed that 1mg of cortisone acetate was equivalent to 0.8mg of hydrocortisone[17] but, there is a large (21% to 95%) variability in bioavailability of cortisone acetate[21] as well as tissue specific expression of 11βHSD1.

Prednisolone[22] has a similar plasma profile to Plenadren and since this is taken on wakening, the 4am anticipatory rise in glucocorticoid does not occur. At a molecular level we know that prednisolone has prolonged binding to the glucocorticoid receptor compared to hydrocortisone, which would be expected to result in different transcriptional responses in glucocorticoid responsive tissues and prolonged effect [23]. Whether this theoretical advantage is clinically useful and results in reduced risk of adrenal crisis is unknown. The rate of adrenal crises has grown with the increased prescription of short-acting glucocorticoids such as hydrocortisone, although a causal link needs to be confirmed[24]. Further data from a prospective observational study in Germany recorded the frequency of crises experienced by patients on different treatment regimens, and showed that the proportion of patients on prednisolone experiencing a crisis was not greater than expected[25]. It is however clear that previously used doses have been excessive and 3mg to 4mg once daily is sufficient replacement in most patients [26,27]. Currently there are two NIHR adopted studies actively recruiting, comparing low-dose prednisolone with standard regimens of hydrocortisone[28,29]. Low dose prednisolone has been shown to be superior in reducing androgens, 17-hydroxy progesterone and improving growth velocity in patients with congenital adrenal hyperplasia compared to thrice daily hydrocortisone [30].

Subcutaneous glucocorticoid infusions

Infusion pumps have been used to mimic the circadian rise in morning cortisol. In addition to normalising morning ACTH levels in patients with primary adrenal failure, improvements in physical functioning and vitality domains of the SF-36 have been noted [31,32]. There are however no further anthropometric or objective benefits, and in double-blind placebo-controlled conditions when compared to oral hydrocortisone treatment, the subjective health outcome benefits are no longer detectable [33]. These studies were performed without any pulsatile or ultradian patterns.

Like many other hormones cortisol is secreted in a pulsatile manner [34,35]. This results in a circadian rhythm that is made up of underlying oscillations which reach maximum amplitude at the time of the circadian peak. In animal models these pulses have been shown to be very important for normal physiological and behavioural activity[36,37]. Although there is relatively little variation of circadian rhythm between subjects, there is much more intra-individual variation in the daily pattern of ultradian pulses[34]. Since the frequency of ultradian pulses simply depends on fixed delays in the feedforward-feedback relationship between the pituitary corticotropes and the adrenal fasciculata cells[38,39] the circadian change in cortisol is determined by changes in pulse amplitude rather than pulse frequency. This provides us with a much easier opportunity to use pumps to replicate physiological pulses, as demonstrated by Russell and colleagues[40].

It is not yet clear to what extent it is important to replicate these rhythms to provide optimal treatment for patients with adrenal failure. Although we know that stress increases the size of ultradian pulses [41,42], there have been no long term studies on the modulation of ultradian rhythmicity in normal daily living. Physiological studies have shown that it is the presence of both peaks and troughs of cortisol that is important for optimal regulation of behaviour and of glucocorticoid and mineralocorticoid receptors in animals [43,44]. We are now testing this in new psychological paradigms in man.

From a patient's perspective infusion pumps are less convenient than tablets. However, the technological advances of new miniature nanopumps either external or with subcutaneous reservoirs will make pumps less intrusive. Kalafatakis and colleagues recently undertook a double-blind randomised crossover study, in which they recruited 15 young males and implemented a "block and replace" approach to cortisol using three distinct regimens to investigate the comparative effects of pulsatility on cognition, emotion and sleep [45]. Participants had their endogenous cortisol secretion blocked using metyrapone and received 20mg of hydrocortisone in three modalities: 1- a subcutaneous pulsatile mode to replicate the ultradian profile; 2- a subcutaneous cutaneous infusion; 3- oral thrice daily replacement, each for a five-day period. The order in which the modalities were administered was randomised.

The study demonstrated that pulsatility directly affects neurological physiology in the non-stressed state, independent of the cumulative glucocorticoid exposure. Specifically, subcutaneous ultradian pulsatile infusions promoted better quality of sleep and improved performance of working memory compared to the continuous infusions, as assessed by a sleep questionnaire and functional tests respectively.

These different patterns of cortisol oscillations also had differential effects on the fMRI and functional connectivity of the brain regions which process emotional responses (amygdala, dorsal striatum, insula and orbitofrontal cortex) – with parallel changes detected in attentional bias to, and recognition accuracy of emotional cues[45].

These data imply that oscillating levels of cortisol are important for physiological regulation of glucocorticoid receptors and post receptor signalling in the brain and for the regulation of mood in man. Whether differences in endogenous patterns of pulsatility in different individuals alters these functions is unknown. The importance of these pulses in longer term replacement therapy in patients with Addison's disease will be clearer once the Medical Research Council PULSES trial is complete (MR/R010919/1).

Neither immediate release hydrocortisone nor any other oral glucocorticoid will ever replace normal ultradian secretion which remains highly variable across individuals.

Conclusion

Long term patient health and cognitive and emotional state as well as patient convenience and compliance are crucial and a balance between a once daily oral dosing, more frequent oral dosing and the requirement of a pump needs to be considered. Currently there are no good studies comparing low dose prednisolone, dual release hydrocortisone (Plenadren, Duocort), delayed release hydrocortisone (Chronocort) and miniature ultradian pumps with three times daily hydrocortisone, using currently understood lower and biologically equivalent doses. We hope that well controlled, relatively long-term double-blind studies will soon be available to allow a rational approach to optimal therapy on an individual patient basis.

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Another strategy available in some countries is the use of dual release hydrocortisone (Plenadren) once daily first thing in the morning. This sustained release preparation fails to replicate the pre-awakening rise in cortisol and we know very little about what happens to blood or tissue levels of cortisol overnight. It relies on continuous absorption of hydrocortisone from the gut which can be variable, a problem that must be guarded against in patients with infectious diarrhoea, when glucocorticoids are crucial [14]. The manufacturers state that Plenadren is commonly associated (> 1 in 10 cases) with gastrointestinal side effects [15].

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shown to be superior in reducing androgens, 17-hydroxy progesterone and improving growth velocity in patients with congenital adrenal hyperplasia compared to thrice daily hydrocortisone [30].

Subcutaneous glucocorticoid infusions

Infusion pumps have been used to mimic the circadian rise in morning cortisol. In addition to normalising morning ACTH levels in patients with primary adrenal failure, improvements in physical functioning and vitality domains of the SF-36 have been noted [31,32]. There are however no further anthropometric or objective benefits, and in double-blind placebo-controlled conditions when compared to oral hydrocortisone treatment, the subjective health outcome benefits are no longer detectable [33]. These studies were performed without any pulsatile or ultradian patterns.

Like many other hormones cortisol is secreted in a pulsatile manner [34,35]. This results in a circadian rhythm that is made up of underlying oscillations which reach maximum amplitude at the time of the circadian peak. In animal models these pulses have been shown to be very important for normal physiological and behavioural activity[36,37]. Although there is relatively little variation of circadian rhythm between subjects, there is much more intra-individual variation in the daily pattern of ultradian pulses[34]. Since the frequency of ultradian pulses simply depends on fixed delays in the feedforward-feedback relationship between the pituitary corticotropes and the adrenal fasciculata cells[38,39] the circadian change in cortisol is determined by changes in pulse amplitude rather than pulse frequency. This provides us with a much easier opportunity to use pumps to replicate physiological pulses, as demonstrated by Russell and colleagues[40].

It is not yet clear to what extent it is important to replicate these rhythms to provide optimal treatment for patients with adrenal failure. Although we know that stress increases the size of ultradian pulses [41,42], there have been no long term studies on the modulation of ultradian rhythmicity in normal daily living. Physiological studies have shown that it is the presence of both peaks and troughs of cortisol that is important for optimal regulation of behaviour and of glucocorticoid and mineralocorticoid receptors in animals [43,44]. We are now testing this in new psychological paradigms in man.

From a patient's perspective infusion pumps are less convenient than tablets. However, the technological advances of new miniature nanopumps either external or with subcutaneous reservoirs will make pumps less intrusive. Kalafatakis and colleagues recently undertook a double-blind randomised crossover study, in which they recruited 15 young males and implemented a "block and replace" approach to cortisol using three distinct regimens to investigate the comparative effects of pulsatility on cognition, emotion and sleep [45]. Participants had their endogenous cortisol secretion blocked using metyrapone and received 20mg of hydrocortisone in three modalities: 1- a subcutaneous pulsatile mode to replicate the ultradian profile; 2- a subcutaneous cutaneous infusion; 3- oral thrice daily replacement, each for a five-day period. The order in which the modalities were administered was randomised.

The study demonstrated that pulsatility directly affects neurological physiology in the non-stressed state, independent of the cumulative glucocorticoid exposure. Specifically, subcutaneous ultradian pulsatile infusions promoted better quality of sleep and improved performance of working memory compared to the continuous infusions, as assessed by a sleep questionnaire and functional tests respectively.

These different patterns of cortisol oscillations also had differential effects on the fMRI and functional connectivity of the brain regions which process emotional responses (amygdala, dorsal striatum, insula and orbitofrontal cortex) – with parallel changes detected in attentional bias to, and recognition accuracy of emotional cues[45].

These data imply that oscillating levels of cortisol are important for physiological regulation of glucocorticoid receptors and post receptor signalling in the brain and for the regulation of mood in man. Whether differences in endogenous patterns of pulsatility in different individuals alters these functions is unknown. The importance of these pulses in longer term replacement therapy in patients with Addison's disease will be clearer once the Medical Research Council PULSES trial is complete (MR/R010919/1).

Neither immediate release hydrocortisone nor any other oral glucocorticoid will ever replace normal ultradian secretion which remains highly variable across individuals.

Conclusion

Long term patient health and cognitive and emotional state as well as patient convenience and compliance are crucial and a balance between a once daily oral dosing, more frequent oral dosing and the requirement of a pump needs to be considered. Currently there are no good studies comparing low dose prednisolone, dual release hydrocortisone (Plenadren, Duocort), delayed release hydrocortisone (Chronocort) and miniature ultradian pumps with three times daily hydrocortisone, using currently understood lower and biologically equivalent doses. We hope that well controlled, relatively long-term double-blind studies will soon be available to allow a rational approach to optimal therapy on an individual patient basis.

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